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Effects of continuous combined conjugated estrogen/ medroxyprogesterone acetate and 17 β -estradiol/ norethisterone acetate on lipids and lipoproteins

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Abstract

Objectives: Various estrogen/progestogen combinations used in hormonal replacement therapy (HRT) have been reported to influence lipid and lipoprotein fractions differently. This motivated a comparative study where the two continuous combined regimens most commonly used in Sweden during the 1990s have been studied regarding effects on lipid profile. **Methods:** In a 1-year prospective, double-blind study, 62 post-menopausal women were randomized to conjugated estrogen (CE), 0.625 mg, and medroxyprogesterone acetate (MPA), 5 mg, or 17 β -estradiol (E2), 2 mg, and norethisterone acetate (NETA), 1 mg. Serum concentrations of lipids and lipoproteins were measured at baseline and after 1 year of treatment. **Results:** Both treatment groups significantly lowered the lipoprotein(a) (Lp(a)) levels. The CE/MPA group showed no significant changes in total cholesterol (TC), high-density (HDL) and low-density lipoprotein (LDL), but a significant increase of triglyceride (TG) levels. The E2/NETA group developed a significant lowering of total cholesterol, HDL, and LDL, but no significant changes of TG levels. The magnitude of change in serum concentrations of total cholesterol, HDL and TG differed significantly between the two treatment groups. **Conclusions:** Continuous combined treatment with CE/MPA and E2/NETA equally lowered Lp(a), an important risk factor for cardiovascular disease in women. Apart from this, the two treatments produced different effects on lipids and lipoproteins, findings that are more delicate to interpret.

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1. Introduction

Estrogens are known to induce beneficial effects on blood lipids and lipoproteins. In theory, this has been looked upon as factors contributing to a reduced risk for arteriosclerosis in post-menopausal women.

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However, if hormonal replacement therapy (HRT) actually protects women from cardiac death is still a matter of debate. In addition, the overall effect of a combination with estrogen and progestogen still needs to be elucidated.

In earlier studies of lipid metabolism, it has been shown that both the dosage and the type of progestogen are of importance for the lipoprotein, cholesterol and triglyceride (TG) fractions. More androgenic progestogens like norethisterone acetate (NETA) from the 19-nortestosterone group may be more prone to increase cholesterol fractions than derivatives of 17-hydroxyprogesterone, e.g. medroxyprogesterone acetate (MPA) [1–3]. Conversely, the less androgenic MPA may not counteract the estrogen influence on triglycerides [4]. Studies directly comparing combinations with MPA and NETA have, to our knowledge, not been done before. As continuous combined HRT is now the most frequently prescribed HRT it was of obvious interest to accomplish a comparative study of the two continuous combined HRT's most commonly used in Sweden during the 1990s. Earlier, lipid changes have been investigated in trials with the two types of HRT separately, and some of the results are described below.

A study by Munk-Jensen et al. [5], showed some decrease of high-density lipoprotein (HDL) with a continuous combination of 17 β -estradiol and norethisterone acetate (E2/NETA). Furthermore, Ylikorkala et al. [6] have shown that E2 in combination with NETA decreased HDL. One study showed almost no counteracting effects of MPA on serum lipid changes induced by conjugated estrogen (CE) alone [7]. In a study by Lobo et al. [7], CE and MPA increased HDL and TG and decreased total cholesterol (TC), low-density lipoprotein (LDL) and serum lipoprotein(a) (Lp(a)) [7]. Finally, comparisons with studies using sequential HRT are hazardous since duration as well as doses of the progestogens used are different. The effects of different estrogens have been reported in a meta analysis by Godsland. CE and E2 produced similar effects on blood lipids and lipoproteins [4].

The purpose of the present study was to compare the effects of a continuous treatment with 0.625 mg conjugated estrogen and 5 mg medroxyprogesterone acetate to 2 mg 17 β -estradiol and 1 mg norethisterone acetate on blood lipid and lipoprotein profiles in post-menopausal women.

2. Material and methods

2.1. Study population

The study was carried out in five gynecological centers in Sweden between March 1997 and January 1999. Sixty-six healthy women with climacteric symptoms were recruited through advertisement or in connection with clinical visits. The inclusion criteria were: healthy women with an intact uterus, aged 52 years or more and being at least 2 years post-menopausal (women who had never used HRT). To include current users, the requirement was that HRT should have been going on for at least 2 years. However, for those women a washout period of at least 2 months before study start was carried out. The exclusion criteria were: adenomatous hyperplasia with or without atypia, undiagnosed vaginal bleeding, history of cancer of any kind, active liver disease, cardiovascular or thromboembolic disease, uncontrolled hypertension, diabetes and chronic medication with barbiturates and antiepileptic or psychiatric drugs such as antidepressants or benzodiazepins. In addition, smokers and women with a body mass index (BMI) above 31 kg/m² were excluded (three women). However, lipid and lipoprotein values outside the normal range at screening did not constitute an exclusion criterion. Finally, 62 women were included in the study. The use of lipid lowering agents, statines, or steroid hormones other than study medication was not permitted during the study period.

At the screening visit, none of the women had taken any drug liable to interfere with lipoprotein metabolism (statines or diuretics) in the 3 months preceding this visit. All the women had normal renal and hepatic function before and during treatment as indicated by routine biochemical tests. In total, three women used anti-hypertension drugs (verapamil, felodipin and atenolol in combinations with enalapril) during the study. Before taking part (screening visit), the women underwent a physical examination, including breast and gynecological examinations. A transvaginal ultrasonography for the determination of endometrial thickness (double-layer technique) and an endometrial biopsy (the results are presented elsewhere) was performed. In case the endometrium was more than 10 mm, the women were not allowed in the study regardless of biopsy result. In addition, blood

pressure, weight and height were measured. Cervical smear and mammography were performed in case results were not available for the year prior to study onset. Blood samples for measuring plasma lipids and lipoproteins, kidney, liver and thyroid function were taken.

2.2. Study procedure

The effect of two different continuous combined regimens of HRT on blood lipids was evaluated in a 1-year prospective, double-blind randomized parallel-group design. The women were daily treated with either conjugated estrogen 0.625 mg and medroxyprogesterone acetate 5 mg or 17 β -estradiol 2 mg and norethisterone acetate 1 mg. Enrollment and randomization were done at the baseline visit. A randomization list in blocks of four was computer generated by a statistician and kit numbers were assigned in ascending order at each investigative visit. In order to keep the medication blinded, a double-dummy technique with dark coated blisters was used. Apoteksbolaget AB, Stockholm, Sweden, performed the randomization and blinding. Novo Nordisk, Denmark, provided the study medication E2/NETA. Pharma-Vinci Medical Production, Frederiksvaerk, Denmark, produced the placebo tablets for E2/NETA. The CE/MPA combination and the corresponding placebo tablets were provided by Wyeth-Ayerst, Philadelphia, USA. Counting the study supplies at each visit assessed compliance.

Adverse events and concomitant medication were documented at each follow-up visit (at 2, 6 and 12 months). Reasons for early discontinuation of the study medication were documented by the investigator in the clinical report form by checking one of the following predefined categories: adverse reaction, other medical event, failed to return, unsatisfactory response—efficacy, protocol violation, other non medical event and patient request unrelated to study. At the last visit (12 months) the clinical examination was repeated, including pelvic and breast examination, transvaginal ultrasonography, endometrial biopsy and blood pressure. Again, a mammography was made. Finally, a blood sample was taken for measuring plasma lipid and lipoprotein, and thyroid function.

The primary outcome measure of this study was changes in blood lipid and lipoprotein patterns dur-

ing long-term treatment with two different continuous combined HRT's.

The study was conducted and monitored according to Nordic Guidelines for Good Clinical Trial Practice (GCP). In addition, Standard Operation Procedures (SOP), defined by the sponsor, was used. The research protocol was approved by the Ethics committee of each center involved and by the Swedish Medical Product Agency following the rules of the Revised Declaration of Helsinki (Hong Kong, 1989).

2.3. Lipid assays

Blood samples from the antecubital vein were obtained under fasting conditions (minimum 12 h overnight) to determine plasma lipid and lipoprotein levels. From the same samples kidney, liver and thyroid functions were assessed. Within a half to one hour, the blood was centrifuged at 3000 revolutions per minute for 10 min. The fresh serum samples were analyzed consecutively within 24 h at one central laboratory, Nova Medical CALAB Clinical Trials Central, St. Görans Hospital, Stockholm, Sweden, and the laboratory procedures fulfilled all criteria for Good Laboratory Practice. Laboratory personnel were blinded to treatment regimen. Normal values from CALAB are presented in Table 2.

Levels of total cholesterol were measured by an enzymatic photometric test using cholesterol oxidase and peroxidase [8,9], and the interassay coefficient of variation was 1.9%. Triglyceride levels were assayed by a colorimetric enzymatic test using glycerol-3-phosphateoxidase [10], and the coefficient of variation was 3.5%. Concentrations of HDL cholesterol was determined by a direct enzymatic method [11] and the concentration of LDL cholesterol was calculated according to the method of Friedewald et al. [12] with an interassay coefficient of variation of 4.7%. Lp(a) concentrations were measured by an immunoturbidimetric analysis [13] with an interassay coefficient of variation of 8.8%.

2.4. Statistical methods

Conventional descriptive statistics are presented. When normality of data could not be rejected according to a Kolmogorov–Smirnov test, one-sample paired and two independent samples *t*-tests were used to analyze the within patient group changes and between

groups comparisons. When a Kolmogorov–Smirnov test yielded statistical significance (indicating non-normality of data) Wilcoxon type non-parametric tests were used. In transition matrices (four field tables), the McNemar test was used for analysis of changes within groups of lipid values from normal to above normal values (or vice versa). If the expected frequency of changes was too small (<5), a binomial test was used [14]. Exploratory, multivariate stepwise backward linear regression analyses have been performed on changes of lipids. The predictors were as follows: baseline lipid levels, age, BMI, diastolic and systolic blood pressure, height, weight, years from last menstruation, and the indicator variables (0/1), treatment.

The mass-significance problem has been assessed using Eklund's rule [15]. The standard statistical computer program Statistical Package for the Social Sciences (SPSS), version 11.0 was used for data handling and analyses. A P -value <0.05 was considered significant.

3. Results

3.1. Baseline characteristics

A total of 62 women were included in the study and the number of women included at the five centers was between 7 and 26. Of these, 47 completed the study ("completers") and 15 dropped out ("dropouts"), 6 mainly due to bleeding problems. Other reasons were headache ($n = 2$), abdominal pain ($n = 2$), afraid to use HRT ($n = 1$), constipation/breast tenderness ($n = 1$), depression ($n = 1$), upper respi-

ratory infection ($n = 1$) and palpitations ($n = 1$). Between completers and dropouts there were no statistically significant differences in demographic data (Table 1) or baseline lipids tests. However, dropouts had significantly higher TSH concentrations compared to completers (2.4 ± 0.33 mU/l versus 1.7 ± 0.16 mU/l, $P < 0.05$).

When comparing the two treatment groups, there were no statistically significant differences of mean baseline characteristics what so ever (Table 1). Twenty-seven women (57.4%) had not been using HRT prior to the study.

3.2. Laboratory tests of thyroid function

Baseline values for thyroid function did not differ between the treatment groups (Table 2). After 1 year, the mean TSH levels were higher in the E2/NETA group than in the CE/MPA group (2.03 ± 0.19 mU/l versus 1.31 ± 0.19 mU/L; $P < 0.001$), however, well below the upper limit for normal values. Serum TSH increased in the E2/NETA group and decreased in the CE/MPA group (0.19 ± 0.131 mU/l versus -0.22 ± 0.154 mU/l (Table 2), although, the difference of change was not significant. At baseline, one woman in the CE/MPA group had a TSH value 48% above the normal reference range. This normalized after 1 year of treatment.

3.3. Changes in blood lipid levels and comparisons between treatment groups

According to tests of normality, data on changes of triglycerides, LDL, and Lp(a) concentrations deviated significantly from normality. Baseline lipid levels did

Table 1

Baseline characteristics (mean \pm S.E.M.) of women treated with conjugated estrogen and medroxyprogesterone acetate (CE/MPA) or 17 β -estradiol and norethisterone acetate (E2/NETA) and who completed the whole study, and the women who dropped out from the study

	CE/MPA ($n = 23$)	E2/NETA ($n = 24$)	Drop outs ($n = 15$)
Age (years)	55.8 ± 0.6	55.1 ± 0.6	57.5 ± 1.1
Time since menopause (years)	4.4 ± 0.5	4.7 ± 0.7	5.4 ± 0.9
Parity (n)	2.0 ± 0.2	1.6 ± 0.3	2.1 ± 0.3
Systolic blood pressure (mm Hg)	131 ± 3	134 ± 3	136 ± 3
Diastolic blood pressure (mm Hg)	75 ± 2	79 ± 2	79 ± 2
BMI (kg/m^2)	25.3 ± 0.5	25.8 ± 0.7	25.7 ± 0.9
Endometrial thickness (mm)	3.3 ± 0.4	2.9 ± 0.2	3.2 ± 0.4

Table 2

Lipid, and thyroid values (mean \pm S.E.M.) at baseline (B) and at final visit (F) for women treated with conjugated estrogen and medroxyprogesterone acetate (CE/MPA) or 17 β -estradiol and norethisterone acetate (E2/NETA). Normal ranges defined by the laboratory used are shown

	Visit	Normal range	CE/MPA (<i>n</i> = 23)	E2/NETA (<i>n</i> = 24)
			Mean \pm S.E.M.	Mean \pm S.E.M.
S-Cholesterol (mmol/l)	B	<6.5	6.1 \pm 0.18	6.5 \pm 0.23
S-Cholesterol (mmol/l)	F		6.1 \pm 0.21	5.9 \pm 0.17
S-Triglycerides (mmol/l)	B	0.6–2.2	1.1 \pm 0.10	1.2 \pm 0.13
S-Triglycerides (mmol/l)	F		1.3 \pm 0.13	1.1 \pm 0.07
S-Lp(a) (g/l)	B	<0.30	0.20 \pm 0.04	0.30 \pm 0.06
S-Lp(a) (g/l)	F		0.13 \pm 0.03	0.20 \pm 0.04
S-HDL (mmol/l)	B	\geq 1.15	1.7 \pm 0.09	1.8 \pm 0.07
S-HDL (mmol/l)	F		1.7 \pm 0.07	1.6 \pm 0.06
S-LDL (mmol/l)	B	<5.0	3.9 \pm 0.18	4.1 \pm 0.25
S-LDL (mmol/l)	F		3.8 \pm 0.20	3.6 \pm 0.19
S-T4, free (pmol/l)	B	12–25	16 \pm 0.40	16 \pm 0.39
S-T4, free (pmol/l)	F		16 \pm 0.39	16 \pm 0.32
S-TSH (mU/l)	B	0.20–5.00	1.6 \pm 0.29	1.8 \pm 0.16
S-TSH (mU/l)	F		1.3 \pm 0.19	2.0 \pm 0.19

not differ between the treatment groups (Table 2). The changes in lipid and lipoprotein profiles during 1 year of treatment are shown in Fig. 1.

Total cholesterol did not change significantly in the CE/MPA treatment group (0.01 ± 0.14 mmol/l), whereas within the E2/NETA group TC decreased significantly (-0.64 ± 0.15 mmol/l, $P < 0.001$). The difference in change between groups was significant ($P < 0.005$).

Mean levels of HDL did not change significantly within the CE/MPA group, whereas a significant decrease ($P < 0.001$) was seen in the E2/NETA group. The difference in change between groups was significant (-0.01 ± 0.04 mmol/l versus -0.18 ± 0.04 mmol/l, $P < 0.01$).

LDL was significantly lowered within the E2/NETA group ($P < 0.025$) whereas no significant change could be seen in the CE/MPA group. When the change in the whole study group was analyzed together there was a significant decrease in LDL levels after 1 year of HRT (-0.31 ± 0.15 mmol/l, $P < 0.05$).

There was a significant increase of TG within the CE/MPA group ($P < 0.001$), whereas in the E2/NETA group no significant change was seen. The difference in change between the two treatment

groups was significant (0.27 ± 0.07 mmol/l versus -0.12 ± 0.11 mmol/l, $P < 0.005$).

Compared to baseline, there was a significant decrease in Lp(a) levels in both treatment groups (CE/MPA: -0.07 ± 0.02 g/l, $P < 0.005$ versus E2/NETA: -0.10 ± 0.04 g/l, $P < 0.001$). However, the difference in change between the two treatment groups was not significant (Fig. 1).

Fig. 1 presents the P -values from 15 significance tests of which eight were significant on at least the 5% level. According to Eklund's rule [15] the results presented are significant on at least a mass-significance level of 2%. The analyses have been performed and results are presented according to the Per-Protocol (PP) principle due to the fact that complementary analyses according to the Intention-To-Treat principle (ITT, using last observation carried forward) did not significantly change the results found.

3.4. Multivariate regression analyses

Treatment and a number of possible predictors for change in blood lipids were used (see Statistical methods). The baseline lipid levels were negatively correlated to the change of all lipids in the regression

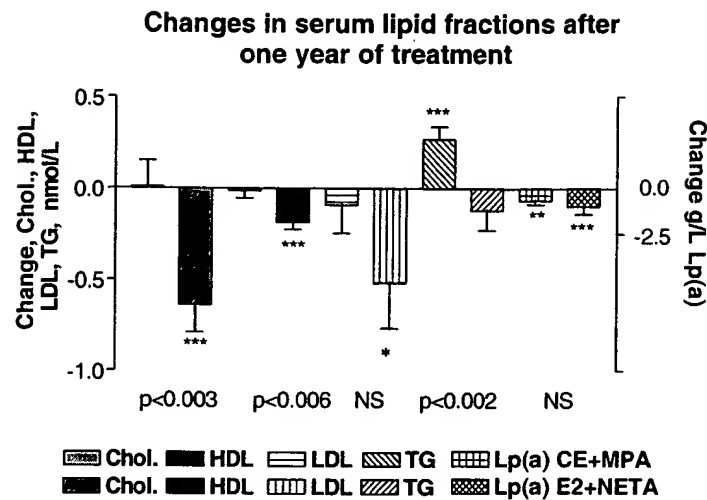


Fig. 1. Mean \pm S.E.M. for changes from baseline of serum lipid and lipoprotein fractions after 1 year of treatment. Chol: total cholesterol (mmol/l); HDL: high-density lipoprotein (mmol/l); LDL: low-density lipoprotein (mmol/l); TG: triglycerides (mmol/l); and Lp(a): lipoprotein(a) (g/l). In the pair of bars, the left bars indicate daily treatment with 0.625 mg conjugated estrogen and 5 mg medroxyprogesterone acetate, (CE/MPA; $n = 23$), and the right bars treatment with 2 mg 17 β -estradiol and 1 mg norethisterone acetate (E2/NETA; $n = 24$). P -values at the bottom of the graph show differences of change between the treatment groups. Significant changes from baseline within the groups are indicated * $P < 0.05$, ** $P < 0.005$, *** $P < 0.001$, at each bar.

analyses ($P < 0.001$ in all tests) indicating that high baseline levels yielded a greater decrease in lipids than low baseline levels. Therefore, the multiple linear regression analyses were performed using change of concentration between baseline value and 1-year value (delta value = final value – baseline value). Treatment was a significant predictor for the change of TC ($P < 0.005$), HDL ($P < 0.005$), and TG

($P < 0.005$) concentrations. After adjustment for the baseline lipid levels and other predictors, the decrease in TC, HDL and TG levels in the E2/NETA group was significantly larger than in the CE/MPA group.

Age was positively correlated to change in TG levels ($P < 0.01$), indicating that older women, compared to younger, had a more pronounced increase in TG levels during the study (Table 3).

Table 3

Results from backward stepwise linear regression analyses on changes of lipid and lipoprotein concentrations after 1 year of treatment

Dependent variable	Predictors	Coefficient \pm S.E.M.	t	$P <$	R^2
Delta TC	Treatment (0/1)	-0.56 ± 0.184	-3.05	0.005	0.42
	BL, Height	-0.03 ± 0.017	-1.98	0.05	
	BL, TC (mmol/l)	-0.34 ± 0.090	-3.80	0.001	
Delta HDL	Treatment (0/1)	-0.15 ± 0.050	-2.97	0.005	0.40
	BL, HDL (mmol/l)	-0.29 ± 0.068	-4.27	0.001	
Delta LDL	BL, LDL (mmol/l)	-0.59 ± 0.118	-5.02	0.001	0.36
Delta TG	Treatment (0/1)	-0.31 ± 0.104	-2.97	0.005	0.52
	BL, Age	0.05 ± 0.018	2.83	0.01	
	BL, TG (mmol/l)	-0.47 ± 0.093	-5.09	0.001	
Delta Lp(a)	BL, Lp(a) (g/l)	-0.52 ± 0.068	-7.67	0.001	0.57

The delta values are computed as final value minus baseline value (BL). TC: Total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; and Lp(a): lipoprotein(a). Treatment is coded 0: CE/MPA and 1: E2/NETA. Coefficient: partial regression coefficients with standard error; S.E.M.: standard error; t : Student's t ; R^2 : coefficient of multiple determination.

3.5. Transition of lipid values

The transition of serum values in and out of the normal range was investigated for all lipid parameters. Only total serum cholesterol showed a significant difference in transition frequency between the treatments. In the CE/MPA group at baseline 16 women were within normal values and 7 above. After 1 year of treatment, 15 women were within normal and 8 above, of which 3 came from the normal baseline group and 5 were still above the normal baseline. Two women had their values normalized. At baseline, in the E2/NETA group, 13 women were within the normal range and 11 above. After 1 year, 19 women were normal and 5 above, whereas 6 women had shifted from increased levels to normal. The change in total cholesterol was significant within the E2/NETA group ($P < 0.05$). During the whole study period, one woman reported a serious adverse event: surgery behind the nose/conchotomized bilaterally. No case of thrombosis was reported.

4. Discussion

The major finding of the present study was that after 1 year of HRT significant differences in total cholesterol, HDL and triglycerides were found in women treated with conjugated estrogens and MPA compared to 17 β -estradiol and NETA. However, a more significant finding was that both treatments effectively reduced Lp(a), which is regarded as an important risk factor for coronary heart disease (CHD) in women. As a matter of fact, the effects of HRT on coronary heart disease in post-menopausal women have, during the last decade, been a matter of debate. Epidemiological data suggest that HRT is associated with a reduction of CHD risk [16]. On the other hand, a significantly increased risk was noted in a recently published large, randomized, placebo controlled trial [17]. One reason for a negative impact on CHD risk might, however, be that other adverse haemostatic or vascular effects of HRT, such as the increased risk for thromboembolism overshadows the beneficial effects obtained by a change in lipid and lipoprotein levels. In addition, secondary prevention of myocardial infarction with HRT has not been successful either [18].

Albeit clinical data are inconsistent at the moment, results concerning individual risk factors are still of interest. In the present study, there was no change in HDL values after 1 year compared to baseline in the CE/MPA group. In contrast, HDL decreased in the E2/NETA group after one year of treatment, and this finding is at odds with previous studies [5,19]. Low levels of HDL-cholesterol in combination with high levels of TG seems to be a predictor for cardiovascular disease in women over 50 years of age [20,21]. In the present study, however, no women displayed low HDL levels in combination with high TG levels.

The incidence of CHD increases after menopause. National Cholesterol Education Program Adult Treatment Panel II (NHANES) has shown that total and LDL-cholesterol is accelerated in women after menopause [22]. Several clinical trials have shown that reducing LDL concentrations lowers the morbidity and mortality from coronary heart disease [22]. The most powerful agent that can reduce LDL levels is estrogen [23–25]. In the present study, a reduction of LDL was found in both treatment groups, but the change did not reach statistical significance in the CE/MPA group.

The changes in lipoproteins due to HRT are discussed in a review article [26]. It has been shown earlier that unopposed estrogen reduces LDL and increases HDL and TG levels in women with normal lipid levels. The reduction of LDL was confirmed in the present study, although only in the E2/NETA group. Compared to previous studies on cyclical HRT, continuous combined treatment was equally efficient in this respect [21]. Estrogens are known to reduce the synthesis of Lp(a) [27]. Independently of lipid changes, Lp(a) is regarded as a strong predictor for cardiovascular disease [3,28]. It has also been shown that the concentrations of Lp(a) are not influenced by external factors, such as exercise and dietary habits [29]. However, data from previous studies on effects of HRT on Lp(a) levels are inconclusive. Stadberg et al. [30] reported no significant effect on Lp(a) with 2 mg E2 and 1 mg NETA [30]. Others have shown that concomitant administration of MPA does not adversely affect an estrogen-induced reduction of Lp(a) concentrations in post-menopausal women [7]. We have shown that both treatment regimens reduce the Lp(a) concentrations.

There are limitations to the present study. When planning the study, 25 women in each treatment group was regarded as sufficient since that number is usually enough for studies on lipid effects. However, a post hoc power analysis on the found differences and standard deviations of differences in lipids between groups revealed that power was too low (<80%) concerning LDL and Lp(a). Thus, true differences between treatment effects that could have been seen in larger samples, might have been missed. Nevertheless, a significant reduction in LDL levels was seen in the E2/NETA group, and a significant reduction in Lp(a) levels in both groups. Another weakness is the drop out frequency, which was larger than expected, in the present study. However, the reasons for dropout (mainly bleeding problems) and the fact that there were no significant differences in baseline lipid values between completers and dropouts makes it hard to believe that the dropouts should have altered the results found.

These two continuous combined HRT's contain different types of estrogens (0.625 mg of CE and 2 mg micronized E2 respectively) but these doses are regarded as equipotent in their biological activity, at least in the endometrium [2,31]. Furthermore, similar effects of CE and E2 on plasma lipoproteins have been demonstrated earlier [32].

In addition to different estrogens, the two combinations used in our study also contained two different progestogens, namely MPA and NETA. To our knowledge, comparative studies of the effects on lipids and lipoproteins by 5 mg of MPA and 1 mg of NETA have not been performed before. It is not known if these two doses are equipotent in this respect. Earlier, high levels of TG in women treated with CE/MPA have been reported [7]. However, the TG increase was smallest in the group treated with continuous CE 0.625 mg/MPA 5 mg compared to lower continuous doses of MPA (2.5 mg), sequential MPA (5 and 10 mg) and CE regimen alone [7]. Estrogen alone tends to increase the concentrations of TG while progestogens, especially derivatives of 19-nortestosterone, a more androgenic progestin, have been reported to reduce the TG levels [33]. In the three large randomized studies, WHI, HERS and PEPI, 2.5 mg MPA and 0.625 mg daily were administered [17,18,24], a combination frequently used in North America. The reason to use 5 mg MPA in the present study was and still is that,

2.5 mg MPA in combination with CE is not registered in Sweden. These clinical trials (WHI, HERS and PEPI) showed a decrease in total cholesterol and LDL, and an increase TG and HDL after 1 year of treatment. The increase in HDL levels during CE/MPA treatment could not be confirmed in the present study. A feasible explanation might be that the MPA dose used by us was higher. However, when combinations with 2.5 and 5 mg MPA were directly compared, no difference in HDL concentrations was noted [7].

Apart from dose differences, other factors might influence effects of HRT on lipids and lipoproteins. A recently published study comparing effects of HRT on lipids and lipoproteins in five European countries has reported national differences in cholesterol, HDL and Lp(a). A majority of the women in the study were treated with transdermal E2/NETA [34]. Conclusions from studies of lipids and lipoprotein metabolism during HRT cannot therefore be generalized to all populations.

There is evidence that HRT could affect thyroid function in post-menopausal women, and impaired thyroid function is known to affect lipid and lipoprotein profiles in a negative respect [35]. In the present study, treatment with E2/NETA reduced levels of HDL and possibly the elevation of TSH in this group could have contributed to this effect. However, this is less likely since both LDL and Lp(a) were reduced by E2/NETA treatment. Also, the levels of TSH were well below the normal range.

Due to the complexity of the interrelationships between the different lipid factors it is extremely difficult to interpret changes in lipid and lipoprotein concentrations during HRT and relate them to other risk factors for cardiovascular disease. The multiple regression analysis in the present study revealed no association between baseline body mass index or blood pressure and changes in lipoprotein levels. It has been suggested, that the addition of a progestogen to the estrogen treatment does not counteract the beneficial effects on lipoproteins in post-menopausal women [3,7]. However, the clinical relevance of this has been questioned after a recently published clinical trial [17]. The results from the present study show some differences between the two treatment groups. After 1 year of HRT significant differences between the two treatment groups regarding TC, HDL and TG were found. The CE/MPA group showed

intermediate changes in lipid profiles and the E2/NETA group exhibited greater changes.

At first site, the E2/NETA combination seems to be more beneficial regarding effects on lipid profile. Especially women with elevated lipid or lipoprotein levels before treatment might benefit more from this combination compared to the CE/MPA treatment. However, the single most important effect is probably the reduction of Lp(a), which was seen in both treatment groups. A finding that further complicates the interpretation of these data was the reduction of HDL seen in the E2/NETA group exclusively. Obviously, further research is needed concerning the effects on lipids of HRT, and (above all) clinical studies comparing effects on CHD with different preparations.

We conclude, that for the time being, none of the HRT combinations compared in this study should be recommended above the other (to women in general). In some cases though, an individualized choice of combination might be preferred based on the results of the study.

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